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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/839,894	04/20/2001	Zeev Altboum	UOFMD.006A	4293

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SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
LUCAS, ZACHARIAH	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/839,894	ALTBOUM ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *82-91 and 94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *82 and 84* is/are allowed.

6)☒ Claim(s) *83, 85-91, 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-20-2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 82-91, and 94 are pending and under consideration in the application. Claims 82-93 were pending in the prior action, mailed on October 21, 2003. Claims 82 and 84 were indicated to be allowable, and claims 83, and 85-93 were rejected. In the Response filed on April 20, 2004, the Applicant cancelled claims 92 and 93; amended claims 83, and 85; and added claim 94.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on April 20, 2004, complies with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

3. It is noted that two of the references listed in the IDS have been crossed out. These references were previously considered and made of record in the IDS of October 4, 2001.

Claim Objections

4. **(Prior Objection- Withdrawn)** Claims 92 and 93 were objected to under 37 CFR 1.75(c), as being of improper dependent form. These claims have been cancelled from the application. The objection is therefore withdrawn.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. **(Prior Rejection- Maintained)** Claims 85-93 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite because the Applicant has not defined what is meant by the phrase "high stringency conditions." The rejection is withdrawn as to cancelled claims 92 and 93, and extended to new claim 94. The Applicant traverses the rejection on the basis that those in the art would understand what such conditions comprise, and that the specification provides examples of such conditions in the specification. However, the phrase "high-stringency" is a relative term, and one of ordinary skill in the art would not know from the present disclosure the scope of stringency conditions the Applicant considers to fall within this scope. The Applicant has not provided sufficient information such that those in the art would be able to determine the scope of what is being claimed. It is suggested that the Applicant draft the claims such that they identify the conditions the Applicant considers highly stringent.

7. **(Prior Rejection- Withdrawn)** Claims 86-93 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims read on an immunogenic composition comprising a substantially pure CsaE protein in combination with a substantially pure CsaB protein or CS4 antigen. The Applicant's arguments in combination with the teachings of the Barry/Levine Declaration are found persuasive. The rejection is therefore withdrawn.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. **(Prior Rejection-Maintained)** Claims 83, and 85-93 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a CsaE polypeptide comprising SEQ ID NO: 10, does not reasonably provide enablement for any polypeptide that is at least 95% homologous thereto. The rejection is withdrawn as to cancelled claims 92 and 93, but is extended over new claim 94. Pending claims 83, 85-91, and 94 read on substantially pure polypeptides with amino acids sequences at least 95% homologous to SEQ ID NO: 10, wherein said polypeptides are capable of inducing a protective immune response to enterotoxigenic Esherichia coli (ETEC). The Applicant asserts that the claims read on a "small genus of polypeptides based on both structural... and functional... features," and that the teachings of the specification and the knowledge of those in the art provides sufficient information to enable those in the art to make and use the claimed invention.

These arguments are not found persuasive. It is first noted that, while the Applicant has established that the CS4 pili is immunogenic in certain animals, and that antibodies to such pili are capable of in vitro inhibition of CS4 agglutination, the Applicant has not provided evidence that the CsaE polypeptide alone is capable of inducing a protective effect. The Applicant has not established what portion of the CS4 pili is targeted by the agglutination inhibiting antibodies, or that animals immunized with the CS4 pili or the CsaE polypeptide are protected from ETEC infection. The teachings of the 2003 Altboum et al. article (Infect Immun 71:1352-60- of record in the April 2004 IDS) are noted. However, while the reference teaches that recombinant

Shigella flexneri cells expressing CS4 were capable of producing an immune response against the pili, and inducing a protective response against S. flexneri (pages 1356-57), the reference does not teach that the composition was capable of protecting immunized animals against ETEC infection. The Applicant has therefore not provided an enabling disclosure for the claimed inventions.

Further, even if the Applicant had established that the CsaE polypeptide provided a protective immune response, the Applicant has not demonstrated what region within the protein is required to perform the required function. As was described in the prior action, with reference to the Bowie and Riffkin references, the art teaches that the effects of modifying a protein sequence are unpredictable, and that modifications to a protein sequence, even outside of the antigenic region, can lead to changes in the proteins immunogenic properties. In the present case, the Applicant has provided neither any examples of operative homologues (i.e. inducing a protective response) of CsaE, nor any information as to what residues within the sequence may be modified without loss of protective function. In order to practice the claimed invention, those in the art would first have to demonstrate that CsaE induced a protective response, then determine what regions or residues of the protein are required for this function, and what if any modifications may be made to the protein without losing the function. While the Applicant requires 95% homology, the Applicant has not provided any guidance as to what 95% is required for function, or provided any indication as where in its sequence the protein may be modified. Thus, even if the Applicant had demonstrated that the CsaE polypeptide itself was capable of inducing a protective response, the Applicant has not provided enabling disclosure for any

homologue of at least 95% that is capable of performing the claimed function. The rejection is therefore maintained over claims 83, 85-91, and 94.

10. **(Prior Rejection- Withdrawn)** Claims 85-93 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make, and/or use the invention. In view of the amendment to the claims, clarifying that the hybridization occurs between the coding sequence of the homologous polynucleotide and the non-coding sequence to SEQ ID NO: 9, the rejection is withdrawn.

11. **(New Rejection-Necessitated by Amendment)** Claims 83, 85-91, and 94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims have been amended/drafted to read on a genus of polypeptides with at least 95% homology to SEQ ID NO: 10, and the function of inducing a protective immune response against ETEC.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical

> and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

In the present application, the Applicant has neither provided examples of homologues of SEQ ID NO: 10, nor demonstrated that SEQ ID NO: 10 itself is capable of inducing a protective immune response. Further, the Applicant has not identified any structure, the presence of which can be correlated to a protective immune response against ETEC. In view of the limited teachings, and the lack of any examples that demonstrate possession of the claimed invention, the Applicant has not provided adequate written description for the claimed genus of inventions.

Claim Rejections - 35 USC § 103

12. **(Prior Rejection –Withdrawn)** Claims 86-93 were rejected in the prior action under 35 U.S.C. 103(a) as being unpatentable over McConnell in view of Cassels. In view of the teachings of the Barry/Levine Declaration and the arguments presented pursuant thereto, the rejection is withdrawn.

Requirement for Information

13. Applicant's response to the Requirement for information, in the form of the Declaration by Doctors Eileen M. Barry and Myron M. Levine, is noted and appreciated.

Conclusion

14. Claims 82 and 84 appear to be allowable.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

James C. Housel 6/14/04
JAMES HOUSEL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600